HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
AVIS
24 JUIN 2020

The legally binding text is the original French opinion version

afamelanotide
SCENESSE 16 mg, implant

First assessment

Key points

Favourable opinion for reimbursement in the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).

What therapeutic improvement?

Therapeutic improvement in management.

Role in the care pathway?

Management is based on light exposure prevention measures (photoprotection by wearing long clothing, mineral sunscreens, etc.), reducing protoporphyrin levels (reducing erythropoiesis by transfusion or administering cholestyramine), and preventing liver damage from progressing to liver failure. There is no etiopathogenic treatment of erythropoietic protoporphyria.

The use of synthetic carotenoids (beta carotene) at a dose varying from 60 to 300 mg/day according to age was previously envisaged in some cases but was abandoned due to insufficient efficacy and possible ocular side-effects. Further treatments associating vitamin C, N-Acetylcysteine, Ramipril,

dihydroacetone have been proposed but their efficacy has not been demonstrated. Narrowband (311 nm) UVB phototherapy has shown some efficacy, but its use remains limited due to heterogeneity in respect of national coverage and the risk of skin cancer.

As liver disease is one of the major risks of EPP, regular liver function monitoring is essential. Erythropheresis, the administration of hydroxyurea (off-label) to inhibit myelopoiesis, and liver transplantation may be envisaged in the treatment of severe cases with liver damage. In view of the risk of recurrence of the disease, which is approximately 60 to 70% at 10 years, bone marrow transplantation (the only potentially curative treatment) may be envisaged, although its benefit/risk ratio has not been demonstrated to date.

Role of the medicinal product in the care pathway

Considering in this context of a rare and severe disease:

- the lack of therapeutic alternative for the prevention of EPP-related phototoxic episodes,
- and the contribution of afamelanotide in management, particularly in terms of quality of life and maintenance under treatment (up to 8 years), objectified by three European observational studies conducted in countries where the product is available,

The Committee deems that SCENESSE (afamelanotide), the only medicinal product to have been granted marketing authorisation in the preventive treatment of phototoxic episodes associated with erythropoietic protophoryia (EPP) has a role in patient care.

The Committee highlights the fact that:

- this medicinal product must only be prescribed by specialists trained on its use and practising in porphyria reference and expert centres,
- the follow-up in terms of efficacy and safety remains limited in clinical studies, as this medicinal product has not been assessed for a period greater than 2 years,
- it is recommended that sun protection measures routinely adopted by each patient to manage their phototoxicity related to EPP and in accordance with their skin type (Fitzpatrick scale) are maintained during treatment with this medicinal product.
- according to the SPC “afamelanotide may induce darkening of pre-existing pigmentary lesions due to its pharmacological effect. A regular full body skin examination (every 6 months) is recommended to monitor all pigmentary lesions and other skin abnormalities. If the skin changes noted are consistent with skin cancer or its precursors, or are ambiguous to the porphyria specialist, dermatology specialist consultation should be sought. The aim is to detect early any skin cancers and their precursors induced by UV exposure, and detect and monitor changes in pigmentary lesions, thus allowing early detection of melanoma”.

Special recommendations

Given the risk of misuse, the Committee reiterates that SCENESSE (afamelanotide) must only be prescribed by specialists trained on its use and practising in porphyria reference and expert centres.

The Committee reiterates that a regular full body skin examination (every 6 months) is recommended to monitor all pigmentary lesions and other skin abnormalities. The aim is to detect early any skin cancers and their precursors induced by UV exposure, and detect and monitor changes in pigmentary lesions, thus allowing early detection of melanoma.

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ Erythropoietic protoporphyria (EPP) results in intense pain associated with phototoxicity, residual skin lesions, and sun avoidance measures having a significant impact on patients' quality of life. The quality-of-life impact associated with phototoxicity has been heavily stressed by patient associations.
◗ SCENESSE (afamelanotide) is a preventive treatment of phototoxic episodes associated with erythropoietic protoporphyria (EPP).
◗ Although its efficacy was deemed to be modest in the pivotal study, the efficacy/adverse effects ratio is substantial in the light of the real-life condition data suggesting an improvement in quality of life and considerable follow-up in respect of maintenance under treatment,
◗ There is no alternative to SCENESSE (afamelanotide) for the prevention of EPP-related phototoxic episodes (see paragraph 05 of this opinion).
◗ In the absence of therapeutic alternatives and despite the weakness of the evidence of its efficacy, SCENESSE (afamelanotide) is the first-line preventive medicinal treatment for EPP-related phototoxicity episodes (see paragraph 08 of this opinion).

Public health impact

Considering:
- the significant impact of EPP on patients' quality of life,
- its very low prevalence,
- the absence of therapeutic alternatives for preventing EPP-related phototoxic episodes and hence the medical need considered to be unmet in this situation,
- the evidence of the superiority of SCENESSE (afamelanotide) over the placebo on pain-free sun exposure time between 10 a.m. and 6 p.m. for 6 months (primary endpoint) with an effect size deemed to be modest,
- a potential impact on the care/life pathway based on European observational data (quality-of-life data and follow-up in terms of maintenance under treatment of up to 8 years), but which is undemonstrated due to a lack of demonstrative evidence,
- the administration regimen of SCENESSE (afamelanotide), involving a visit to the reference centre every 2 months,
- and the partial response to the identified unmet medical need,

SCENESSE (afamelanotide) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of SCENESSE (afamelanotide) is substantial in the MA indication.

The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the MA indication(s) and dosages.

Clinical Added Value

Considering:
- **the evidence of the superiority of SCENESSE (afamelanotide) over the placebo on pain-free sun exposure time between 10 a.m. and 6 p.m. for 6 months (primary endpoint) with an effect size deemed to be modest (median increase in exposure of 24 hours over 6 months, i.e. approximately 8 minutes per day) in a double-blind randomised study on 94 patients with EPP,**
- **real-use condition data which, subject to the inherent limitations of this type of study, suggested the efficacy of afamelanotide in terms of sun exposure (suggested maximum increase of 52 minutes per day), quality of life, and maintenance under treatment (up to 8 years),**

- **the absence of alternatives for preventing EPP-related phototoxic episodes and hence the medical need considered to be unmet in this situation,**
  and despite:
- **the lack of robust long-term efficacy and safety data in clinical studies,**
- **the exploratory and non-demonstrative nature of the endpoints in the pivotal study in respect of quality of life, which is particularly regrettable in this disease,**

the Transparency Committee considers that SCENESSE (afamelanotide) provides a minor clinical added value (CAV IV) in the care pathway of adult patients with erythropoietic protoporphyria (EPP).